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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,295	01/14/2004	Axel Riedel	1/1442	4516

28501 7590 02/22/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
02/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,295	RIEDEL ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 7-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 7-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2 and 7-18 are presented for examination.

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment and submission filed November 30, 2007 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 2 and 7-18 remain pending and under examination. Claim 2 is amended.

Applicant's arguments, filed November 30, 2007, have been fully considered. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

(New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Present claim 12 is directed to a method for the prevention or treatment of asthma, bronchitis, etc.

in a mammal comprising administering a pharmaceutical composition comprising telmisartan or one of the salts thereof and atorvastatin, wherein the HDL blood levels are less than 40 mg/dl for a female human or less than 50 mg/dl for a male human, and further wherein the atorvastatin or a polymorph or salt thereof is administered orally in a daily dose of about 0.018 mg/kg body weight to about 6.43 mg/kg body weight and the telmisartan or salt thereof is administered orally in a daily dose of about 0.143 mg/kg to 7.143 mg/kg body weight. Present claim 13 is directed to substantially similar subject matter, but further defines parenteral administration of atorvastatin or a polymorph or salt thereof in a daily dose of about 0.286 mg/kg body weight and telmisartan or salt thereof in a daily dose of about 0.286 mg/kg body weight.

In particular, the specification as originally filed fails to provide adequate written description for polymorphs of atorvastatin (claims 12-13).

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications* under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure…" *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of

DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant's claims specify the use of atorvastatin, or salts of polymorphs thereof, which is supported by the specification at page 22, lines 23-27, which states, "Atorvastatin is described for example in EP 0247633 and US 4,681,893. Polymorphs of atorvastatin are described for example in WO 97/03958, WO 97/03959, EP 0848704 and EP 1148049. Salts of atorvastatin (monopotassium salt, monosodium salt, calcium salt, magnesium salt, zinc salt and meglumine) are described for example in EP 0409281 and US 5,273,995."

Despite this disclosure, however, Applicant has failed to provide any structural characteristics, description of the crystalline form, such as, e.g., by describing the particular lattice configuration, name(s) or physical properties, such as electron, single crystal, or powder X-ray diffraction patterns or the like, that would provide adequate written description of the polymorphic forms of atorvastatin that Applicant was actually in possession of, and intended to be used within the context of the present invention, at the time of the present invention. Accordingly, such disclosure, while noted, does not provide a teaching of what compounds other than atorvastatin *per se* recited in the specification (and salts thereof) would have been considered within the scope of polymorphic forms as presently claimed such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by the phrase "or polymorph thereof".

While it may be construed that the fact that the polymorphic compound is ultimately the same chemical composition, but arranged via a different crystalline lattice structure, implies a similarity in chemical properties that would be sufficient to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, it is herein noted that Applicant has failed to provide any description, such as, e.g., single crystal or powder X-ray diffraction patterns, of the ultimate structural characteristics of those polymorphic forms that are considered within the scope of those compounds intended for use by

Applicant. The mere fact that the compound may ultimately share the same chemical formula as that of the parent atorvastatin is not sufficient to provide an adequate description of the genus of polymorphs intended by Applicant for use in the present invention, since it is known that polymorphs do not differ in chemical formula, but rather differ, and at times significantly, in the crystalline arrangement (i.e., structural form). In the absence of such a description of the polymorphic forms as present claimed, Applicant's limitation to "or polymorph thereof" is not sufficiently supported by the present disclosure in such a way as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

Furthermore, this information regarding the polymorphs of atorvastatin is essential subject matter for the practice of the instant invention and cannot be properly incorporated into the instant specification by reference to foreign patents and/or publications for such essential subject matter. Applicant is reminded that the incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or, in the instant case, to a publication, is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. Please see 37 C.F.R. 1.57(f).

While it is recognized that adequate written description of a limitation is not required to be stated *in haec verba* in the specification or claims as originally filed, adequate written support for all claim limitations must arise from either an explicit or an implicit suggestion by the disclosure to show that such a concept as now claimed was actually in possession of the Applicant at the time of the invention. For the reasons provided *supra*, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means that fully set forth the claimed invention, in such a way to reasonably convey to one skilled in the relevant art that Applicant had

possession of the concept of employing polymorphic forms of atorvastatin as presently claimed.

Accordingly, claims 12-13 fail to meet the requirements of 35 U.S.C. 112, first paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

(New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 7-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of asthma, bronchitis, interstitial lung disease, insulin resistance, prediabetes, type 2 diabetes mellitus, metabolic syndrome or hypertension combined with hyperlipidemia or atherosclerosis comprising the administration of telmisartan (or a salt thereof) with atorvastatin (or a salt thereof), does not reasonably provide enablement for (1) the prevention of such conditions via the administration of telmisartan (or a salt thereof) with atorvastatin (or a salt thereof) or (2) the use of an atorvastatin polymorph in combination with telmisartan for the prevention or treatment of the claimed disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

For the purposes of consideration under 35 U.S.C. 112, first paragraph, the instant rejection focuses on the particular condition of metabolic syndrome, as recited in present claim 2. However, the reasons stated here concerning the burden of enabling the prevention of the prediabetic condition of metabolic syndrome apply also to myriad of other conditions encompassed by the present claims, but for the obvious difference in the type of disorder.

The presently claimed invention is directed to a method for the prevention or treatment of asthma, bronchitis, interstitial lung disease, insulin resistance, prediabetes, type 2 diabetes mellitus, metabolic syndrome or hypertension combination with hyperlipidemia or atherosclerosis in a mammal comprising administering a pharmaceutical composition comprising telmisartan or one of the salts thereof and atorvastatin (see, e.g., claim 1). Use of polymorphs of atorvastatin is provided for in instant claims 12-13.

Lack of Enabling Direction for Prevention of, e.g. Metabolic Syndrome (Claims 2 and 7-13)

In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the prevention of metabolic syndrome, by administering a pharmaceutical composition of telmisartan or a salt thereof with atorvastatin (or a salt of polymorph thereof), could actually be achieved. Based upon the state of the art, as discussed below, the artisan would have only accepted that the treatment of such a condition could be achieved with this specific combination of agents.

As set forth in *In re Marzocchi et al.,* 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and

using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The present claims circumscribe a method for preventing metabolic syndrome by administering a pharmaceutical composition of telmisartan (or a salt thereof) with atorvastatin (or a salt or polymorph thereof). That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering this combination of telmisartan and atorvastatin, patients would be protected against developing such a disorder. In other words, the skilled artisan would have understood the term "prevention", in its broadest reasonable interpretation consistent with MPEP §2111, to mean that the incidence of developing such a condition would be essentially 0% and could be reasonably expected not to occur. Because such absolute success is not reasonably possible with most diseases or disorders, especially a condition as complex and poorly understood as metabolic syndrome, the specification, which lacks any direction or guidance as to how prevention of metabolic syndrome could actually be achieved, is viewed as lacking an enabling disclosure of the entire scope of the claimed invention.

Regarding the prevention of metabolic syndrome, the objective truth that such a condition may be prevented is doubted because the art expressly recognizes the complex nature and poor understanding of this syndrome and the predisposing factors that characterize this condition.

In this regard, Grundy ("Metabolic Complications of Obesity", Endocrine, 2000) is cited. Applicant's attention is drawn particularly to the abstract, which states, "The rising prevalence of obesity is accompanied by an increasing number of patients with the metabolic complications of obesity. The

major complications come under the heading of the metabolic syndrome. This syndrome is characterized by plasma lipid disorders (atherogenic dyslipidemia), raised blood pressure, elevated plasma glucose, and a prothrombotic state. The clinical consequences of the metabolic syndrome are coronary heart disease and stroke, type 2 diabetes and its complications, fatty liver, cholesterol gallstones, and possible some forms of cancer. At the heart of the metabolic syndrome is insulin resistance…Obesity is the predominant factor leading to insulin resistance, although other factors play a role. The mechanistic link between insulin resistance and the metabolic syndrome is complex. The relationship is modulated by yet other factors, such as physical activity, body fat distribution, hormones, and a person's genetic polymorphic architecture. A better understanding of the molecular basis of this relationship is needed…In addition, understanding at the clinical level will lead to improved management of these complications."

Given that the art expressly acknowledges that the condition of metabolic syndrome and insulin resistance (the primary condition that characterizes metabolic syndrome and results in impaired glucose utilization) as being complex, the skilled artisan would have recognized that the state of the art with regard to metabolic syndrome is not well defined, and is, therefore, unpredictable, such that one of ordinary skill in the art would not accept on its face Applicant's statement that metabolic syndrome could be prevented because the pathophysiology of such a condition is not particularly well characterized. In light of such, the artisan would have required sufficient direction as to how the administration of the presently claimed combination of active agents could actually prevent the development of metabolic syndrome and the patient population in need of prevention could have been readily identified without requiring an undue level of experimentation such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected give that absolute prevention is an outcome not reasonably expected by one of ordinary skill in the art and, further, Applicant has failed to provide any guidance as to how such a population of patients would be identified

such that the presently claimed combination of agents could actually be used for achieving the objective of prevention. Absent this disclosure, the present specification fails to enable the full scope of this invention as it relates to the objective of prevention and, thus, fails to rebut the presumption of unpredictability in the art with regard to this same objective.

Furthermore, given the breadth of conditions characterizing metabolic syndrome (i.e., plasma lipid disorders (atherogenic dyslipidemia), raised blood pressure, elevated plasma glucose, and a prothrombotic state), prevention or prophylaxis against metabolic syndrome would necessarily involve preventing each one or more of the conditions known to be associated with such a syndrome. Such a situation would require the skilled artisan to determine whether the active agents of the present claims are effective in preventing any one or more of these conditions and such a process would amount to undue experimentation, given the breadth and disparate nature of each of these conditions and the poor clinical understanding of metabolic syndrome in general.

Moreover, despite the fact that the art recognizes particular pathophysiological manifestations that contribute to the development of metabolic syndrome (see Grundy, citation *supra*), the fact that a patient may exhibit any one or more of such symptomatic complications does not necessarily mean that the patient is predisposed to developing metabolic syndrome. It is the occurrence and interaction of multiple physiological symptoms, as well as other physiologic factors, such as obesity, genetic conditions and/or predispositions, body fat distribution, etc., that contribute to the development of the condition. Accordingly, the circumstances of each individual patient must be carefully considered when determining patients in need of metabolic syndrome prevention. In other words, the variability among patients precludes a common, art-accepted protocol for metabolic syndrome prevention in all patients, given that each patient has risk factors or circumstances unique to that individual, which must be taken into consideration when determining the most effective approach to prevention of metabolic syndrome.

It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of

enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involves the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

Applicant's instant specification conspicuously lacks any disclosure or teaching of manner and process of using the presently claimed combination of telmisartan and atorvastatin for achieving the objective of prevention of metabolic syndrome. Nowhere does the specification disclose how those patients in need of prevention of metabolic syndrome could be identified, what criteria would be used to determine such patients and how they would be treated using the presently claimed combination of agents such that the skilled artisan would have been imbued with at least a reasonable expectation of success in determining such patients without the burden of an undue level of experimentation. Due to the unpredictable nature of the pathophysiological manifestations of metabolic syndrome and the poor clinical understanding of this condition in the art, as well as the absence of any guidance or direction as to how the skilled artisan would go about identifying patients in need of prevention, the instant disclosure is viewed as lacking enablement for this aspect of the present invention.

In light of these reasons, it is clear that the present specification fails to provide adequate guidance as to how one skilled in the art would accomplish the objective of preventing metabolic syndrome, given what is disclosed in the present specification. Given the highly unpredictable state of the art and, furthermore, given that Applicant has failed to provide adequate guidance or direction as to how to practice the full scope of the presently claimed invention without undue experimentation, the specification lacks any basis for claiming the prevention of metabolic syndrome without obligating the

skilled artisan to perform an undue level of experimentation in order to determine how such an aspect of the invention would actually be practiced. For these reasons, Applicant has failed to obviate the presumption of unpredictability in the art.

Lack of Enabling Direction for the Use of Atorvastatin Polymorphs (Claims 12-13)

The present claims circumscribe a method for the prevention or treatment of asthma, prediabetes, metabolic syndrome, etc. in a mammal, comprising administering a pharmaceutical composition comprising telmisartan or one of the salts thereof and atorvastatin, wherein atorvastatin may also be used in salt or polymorphic form (see, e.g., claims 12-13). However, given the discussion presented in the instant disclosure and in consideration of the state of the art at the time of the invention, one of ordinary skill in the art would have been highly skeptical to anticipate a consistent, or substantially similar, level of therapeutic activity from polymorphic forms of atorvastatin and, therefore, would have been skeptical to anticipate the same efficacy in treating the claimed conditions using polymorphic forms of the same.

The state of the art at the time of the invention with regard to polymorphic forms of organic molecules was sufficiently unpredictable that the skilled artisan would have been skeptical to assume that any polymorphic form of the claimed atorvastatin compound would have the same level of therapeutic activity such that any polymorphic form would be capable of achieving the claimed objective.

In support of this conclusion, Vippagunta et al. ("Crystalline Solids", *Advanced Drug Delivery Reviews*, 48(2001):3-26) is cited. Vippagunta et al. teaches, "The common crystalline forms found for a given drug substance are polymorphs and solvates. Crystalline polymorphs have the same chemical composition but different internal crystal structure and, therefore, *possess different physico-chemical properties*. The different crystal structures in polymorphs arise when the drug substance crystallizes in different crystal packing arrangement and/or different conformations. The occurrence of polymorphism is quite common among organic molecules, and a large number of polymorphic drugs compounds have been noted and catalogued." (p.4, col.1, para.2)

Vippagunta et al. goes on to teach, "Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, tabletability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color [12]. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products [13], while differences in solubility may have implications on the absorption of the active drug from its dosage form [14], by affecting the dissolution rate and possibly the mass transport of the molecules…It is very important to control the crystal form of the drug during the various stages of drug development, because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a sold drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics [15]." (para. bridging col.2 of p.4 and col.1 of p.5)

This well-recognized unpredictability in the form and function of drug polymorphs must be taken into consideration when determining whether a disclosure provides sufficient enabling direction for the use of polymorphic forms with the reasonable expectation that such forms would provide the same, or at least substantially similar, therapeutic efficacy required by the claim without a need for extensive and speculative testing of various polymorphic forms to determine their stability and therapeutic activity and whether such stability and activity can be retained throughout execution of a pharmaceutical formulation process. As directed by the MPEP, the amount of guidance required to be present in the specification as originally filed is directly proportional to the amount of knowledge in the art as well as the unpredictability in the art. In other words, if little or nothing is known in the prior art about an aspect of the claimed invention and the art is unpredictable, the specification needs more detail and guidance as to how to use the invention in order to be enabling. Please reference *In re Fisher*, 417 F.2d 833, 839, 166

USPQ 18, 23 (CCPA 1970) and *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

Applicant's specification fails to provide any disclosure of polymorphic forms that may be used in the context of the claimed invention, let alone any evidence or reasoning as to why one of skill in the art would have been imbued with a reasonable expectation of success in achieving the claimed therapeutic objective using any polymorphic form of atorvastatin. In fact, the known variability in function, stability and bioavailability of various polymorphic drug forms precludes the generalized conclusion that any polymorphic form would be capable of achieving the claimed effect, absent any criteria, identification of such intended polymorphic forms, or evidentiary basis upon which to rely. As a result, the skilled artisan would not have been able to determine what polymorphic forms within the scope of those intended by Applicant would reasonably have possessed the claimed effect and, thus, would have been amenable for use in achieving the claimed therapeutic objective. In other words, the skilled artisan would have no alternative recourse but the undue burden of experimentation in order to determine those polymorphs that could be used, with at least a reasonable expectation of success, in the presently claimed method.

It is well settled in patent law that in cases involving chemicals and chemical compounds, which differ radically in their properties, it must appear in an Applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result. Please reference *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940). The failure of the specification to even identify one polymorphic form that may be used clearly lacks enabling guidance for the entire vast scope of polymorphs of atorvastatin presently claimed without any evidence or reasoning by Applicant addressing the unpredictability in the pharmaceutical and medical arts. While the lack of working embodiments cannot be the *sole* factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the

unpredictable nature of the art and the limited direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

Furthermore, this information regarding the polymorphs of atorvastatin is essential subject matter for the practice of the instant invention and cannot be properly incorporated into the instant specification by reference to foreign patents and/or publications for such essential subject matter. Applicant is reminded that the incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or, in the instant case, to a publication, is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. Please see 37 C.F.R. 1.57(f).

It is noted that Applicant is not required to enable each an every single embodiment encompassed by the claims. While the scope of the required enablement varies inversely with the degree of unpredictability involved, even in the unpredictable arts, such as pharmaceuticals and medicine, a disclosure of every operable species is not required. However, while a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, [please see *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971)], in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species, or even a lack of disclosure of even a single species, usually does not provide an adequate basis to support generic claims. Please reference *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. Please reference *In re Fisher*,

427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species what other species will work. Please see MPEP §2164.03. In the absence of additional disclosure, the skilled artisan would be required to perform an undue level of experimentation in order to determine these other species that would be capable of performing the claimed method.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice this aspect of the invention would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that prevention of the claimed disorders could be achieved using telmisartan or a salt thereof in combination with atorvastatin or a salt or polymorph thereof. In order to actually achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the embodiments of the presently claimed invention.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 7-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 2 is directed to a method for the prevention or treatment of asthma, bronchitis, interstitial lung disease, insulin resistance, prediabetes, type 2 diabetes mellitus, metabolic syndrome or hypertension combined with hyperlipidemia or atherosclerosis in a mammal comprising administering a pharmaceutical composition comprising telmisartan or one of the salts thereof and atorvastatin.

In particular, it is unclear to whom or what the instantly claimed pharmaceutical composition is administered. The claim does not recite the host that is receiving the administration of the composition. Accordingly, one of ordinary skill in the art would not have been reasonably apprised of the scope of the subject matter for which Applicant is seeking protection.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 2 and 7-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 2 is directed to a method for the prevention or treatment of asthma, bronchitis, interstitial lung disease, insulin resistance, prediabetes, type 2 diabetes mellitus, metabolic syndrome or hypertension combined with hyperlipidemia or atherosclerosis in a mammal comprising administering a pharmaceutical composition comprising telmisartan or one of the salts thereof and atorvastatin.

In particular, it is unclear whether Applicant is claiming the prevention or treatment of (1) hypertension combined with hyperlipidemia or atherosclerosis (i.e., hypertension combined with hyperlipidemia or hypertension combined with atherosclerosis) or (2) hypertension combined with hyperlipidemia *or* atherosclerosis (i.e., hypertension combined with hyperlipidemia or atherosclerosis as a separate condition unrelated to the hypertension). In other words, the claims fail to clearly set forth whether the phrase "hypertension combined with" modifies both "hyperlipidemia" and "atherosclerosis" or whether atherosclerosis is intended to be listed as a separate condition unrelated to the recited hypertensive disorder. As a result, one of ordinary skill in the art would not have been reasonably apprised of the scope of the subject matter for which Applicant is presently seeking protection.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 12 is directed to a method for the prevention or treatment of asthma, bronchitis, etc. in a mammal comprising administering a pharmaceutical composition comprising telmisartan or one of the salts thereof and atorvastatin, wherein the HDL blood levels are less than 40 mg/dl for a female human or less than 50 mg/dl for a male human, and further wherein the atorvastatin or a polymorph or salt thereof is administered orally in a daily dose of about 0.018 mg/kg body weight to about 6.43 mg/kg body weight and the telmisartan or salt thereof is administered orally in a daily dose of about 0.143 mg/kg to 7.143 mg/kg body weight. Present claim 13 is directed to substantially similar subject matter, but further defines parenteral administration of atorvastatin or a polymorph or salt thereof in a daily dose of about 0.286 mg/kg body weight and telmisartan or salt thereof in a daily dose of about 0.286 mg/kg body weight.

In particular, there is insufficient antecedent basis for the limitation "the atorvastatin or a polymorph or salt thereof" in lines 1-2 of each of the claims, since the claims from which each of claims 12-13 depend fail to set forth any reference to "atorvastatin or *a polymorph or salt thereof*" *per se*.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2 and 7-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over De Gasparo et al. (WO 01/76573; 2001) in light of Robl et al. (U.S. Patent Application Publication No. 2002/001334; January 31, 2002), cited to show a fact, in view of Cecil's Textbook of Medicine (2000), Harlan et al. (U.S. Patent Application Publication No. 2001/0006656; July 2001) and Bohm et al. (WO 02/15891; February 2002), each already of record, for the reasons of record set forth at pages 4-8 of the previous Office Action dated November 27, 2006, of which said reasons are herein incorporated by

reference.

Applicant traverses the instant rejection, stating that De Gasparo et al. fail to disclose the specific combination of telmisartan and atorvastatin anywhere in the reference. Applicant further alleges that De Gasparo et al. lists a number of commercially available sartans, including telmisartan, but fails to disclose this specific compound "as a selected compound in the context of a specific combination, much less with atorvastatin" (p.4, Remarks). In fact, Applicant submits that the only sartan mentioned in the reference in the context of a specific combination is valsartan, which Applicant alleges constitutes a teaching away from the use of telmisartan. Applicant makes the same allegations with regard to atorvastatin, stating that the compound is not mentioned in combination with telmisartan and that the disclosed combination of atorvastatin with valsartan teaches away from its use with telmisartan. Applicant submits that the secondary references, i.e., Robl et al., Cecil's Textbook of Medicine, Harlan et al. or Bohm et al., do not provide motivation, reasonable expectation of success, or a teaching or suggestion of all of the claim limitations of the invention. Still further, Applicant submits that neither the primary nor the secondary references teach or suggest telmisartan increases the expression of genes regulated by the PPAR-gamma receptor, which is the reason that telmisartan is a preferred combination partner for atorvastatin in the treatment of, e.g., diabetes.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

In response, Applicant's attention is once again directed to pages 17-18 of the Office Action dated March 31, 2006, which sets forth the teachings of De Gasparo et al. insofar as the reference expressly teaches the combination of an AT1-receptor antagonist in combination with an HMG-CoA reductase inhibitor (p.1, l.27-29), wherein the AT1-receptor antagonist is selected from telmisartan (p.3, l.22) and the HMG-CoA reductase inhibitor is selected from atorvastatin (p.5, l.9-11). De Gasparo et al. clearly contemplates embodiments of the invention wherein the combination of at least two therapeutic components comprises an AT1-receptor antagonist (of which telmisartan is expressly disclosed) or a

pharmaceutically acceptable salt thereof, and an HMG-CoA reductase inhibitor (of which atorvastatin is expressly disclosed) or a pharmaceutically acceptable salt thereof. Please reference p.1, p.3, l.22, and p.5, l.9-11 of De Gasparo et al. This teaching is clear, exact and unequivocally speaks to the contrary of Applicant's traversal that the reference fails to disclose the claimed combination.

Applicant appears to be of the persuasion that the lack of a specific example of the disclosed combination of telmisartan and atorvastatin somehow constitutes a complete lack of teaching of the claimed combination and/or constitutes a teaching away from the claimed combination in view of the fact that other combinations of agents are exemplified. This is not persuasive. A preferred or exemplified embodiment (in this case, compositions using valsartan) does not constitute a teaching away from other embodiments disclosed within the four corners of the reference, including non-preferred embodiments. Applicant is reminded that the disclosure of a reference must be considered as expansively as is reasonably possible to determine the full scope of the disclosure and, as a result, is most certainly not limited to that which is preferred and/or exemplified. Please see MPEP at §2123, which states, "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including non-preferred embodiments…Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments." Thus, the fact that other compounds may be exemplified or preferred does not negate or direct the artisan away from the broader teaching of the reference, which expressly provides for, and, thus, clearly contemplates the use of, a combination of an AT1-receptor antagonist (i.e., telmisartan) with an HMG-CoA reductase inhibitor (i.e., atorvastatin). Moreover, Applicant is reminded that there is no legal requirement that a reference *must exemplify* a particular embodiment in order to constitute a teaching of the same. A reference will constitute a teaching so long as the disclosure clearly describes and enables such an embodiment, which, in the present case, such description is clearly found in De Gasparo et al.

Applicant's additional attempt to patentably distinguish the claimed invention over that of the

prior art by asserting that neither the primary nor the secondary references teach or suggest that telmisartan increases the expression of genes regulated by the PPAR-gamma receptor is, as before, not persuasive. The fact that Applicant has recognized another advantage of the combination of telmisartan and atorvastatin, when the prior art already acknowledges the desirability of this same combination for the identical therapeutic objectives as presently claimed, cannot be the basis for patentability. Please see *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The explanation of an effect obtained when using a compound cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In the instant case, even if De Gasparo et al., did not recognize the advantageous effect on increasing expression of genes regulated by PPAR-gamma when telmisartan and atorvastatin were combined, the fact that Applicant has recognized this advantage is not considered a new therapeutic application because the known treatment of the same diseases as presently claimed using this combination of active agents was already known and recognized in the prior art. Though mechanisms of action of chemical entities are no doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 103 is based upon the therapeutic applications and effects of the compounds, not the mechanism by which they exert such a therapeutic effect.

Applicant again states that "none of Robl et al., Cecil's Textbook of Medicine, Harlan et al., or Bohm et al. provide what De Gasparo et al. lacks in providing to one of skill in the art as a motivation, reasonable expectation of success, or teaching or suggestion of all of the claim limitations of the claimed invention" (p.5, Remarks), which is also, as before, not persuasive. The record clearly indicates that one of ordinary skill in the art would have been motivated to combine the cited references in such a manner to render the presently claimed invention *prima facie* obvious with a reasonable expectation of success in making such a combination, absent factual evidence to the contrary, and Applicant has failed to provide any factual evidence to the contrary. Applicant's attention is directed to pages 16-22 of the rejection

presented in the previous Office Action dated March 31, 2006 for this reasoning, which will not be repeated herein so as not to burden the record.

Additionally, Applicant is again reminded that rejections made under 35 U.S.C. 103(a) are based upon the combination of references. As a result, focusing solely on the discrete teachings of each of the cited references is tantamount to examining each of them inside of a vacuum and fails to be persuasive in establishing non-obviousness because it is the *combined* teachings that are the basis for a proper conclusion of obviousness, not each individual reference alone. In other words, it must be remembered that the references are relied upon in combination and are not meant to be considered separately. To properly conclude obviousness of an invention *does not require the claimed invention to be expressly suggested in its entirety by any one single reference under 35 U.S.C. 103(a)*. Rather, the test is *what the combined teachings* of the references would have suggested to those of ordinary skill in the art. Please reference *In re Young*, 403 F.2d 754, 159 USPQ 725 (CCPA 1968) and *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

For these reasons, and those previously set forth at pages 4-8 of the Office Action dated November 27, 2006, rejection of claims 2 and 7-18 remains proper and is **maintained**.

Double Patenting

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2 and 7-18 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1 and 8-35 of U.S. Patent Application No. 10/757,015, in view of Harlan et al. (U.S. Patent Application Publication No. 2001/0006656; 2001), each already of record, for the reasons of record set forth at pages 8-9 of the previous Office Action dated November 27, 2006, of which said reasons are herein incorporated by reference.

In view of the fact that Applicant has failed to file a Terminal Disclaimer over the cited copending application, and further in view of the fact that Applicant has failed to present any arguments or remarks directed to the propriety of the rejection set forth *supra*, the provisional rejection made under the judicially created doctrine of obviousness-type double patenting remains proper and is **maintained**.

Claims 2, 7-11 and 14-18 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-10, 12-15 and 18-25 of U.S. Patent Application No. 10/899,784, already of record, for the reasons of record set forth at pages 9-10 of the previous Office Action dated November 27, 2006, of which said reasons are herein incorporated by reference.

In view of the fact that Applicant has failed to file a Terminal Disclaimer over the cited copending application, and further in view of the fact that Applicant has failed to present any arguments or remarks directed to the propriety of the rejection set forth *supra*, the provisional rejection made under the judicially created doctrine of obviousness-type double patenting remains proper and is **maintained**.

Claims 2, 7 and 12-18 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-21 of U.S. Patent No. 11/300,947 in view of Drug Facts and Comparisons (1996), each already of record, for the reasons of record set forth at pages 10-12 of the previous Office Action dated November 27, 2006, of which said reasons are herein incorporated by reference.

In view of the fact that Applicant has failed to file a Terminal Disclaimer over the cited copending application, and further in view of the fact that Applicant has failed to present any arguments or remarks directed to the propriety of the rejection set forth *supra*, the provisional rejection made under the judicially created doctrine of obviousness-type double patenting remains proper and is **maintained**.

Conclusion

Rejection of claims 2 and 7-18 remains proper and is **maintained**.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

February 10, 2008

/Ardin Marschel/
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